Anemia management in heart failure patients

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Outline

- The Impact of Anemia on the Prognosis of Chronic Heart Failure
- Drug contributing to failure of anemia management in heart failure
- Management of anemia in acute decompensated heart failure
- Management of anemia in chronic heart failure
- Future research

The Impact of Anemia on the Prognosis of Chronic Heart Failure

A Meta-Analysis and Systemic Review

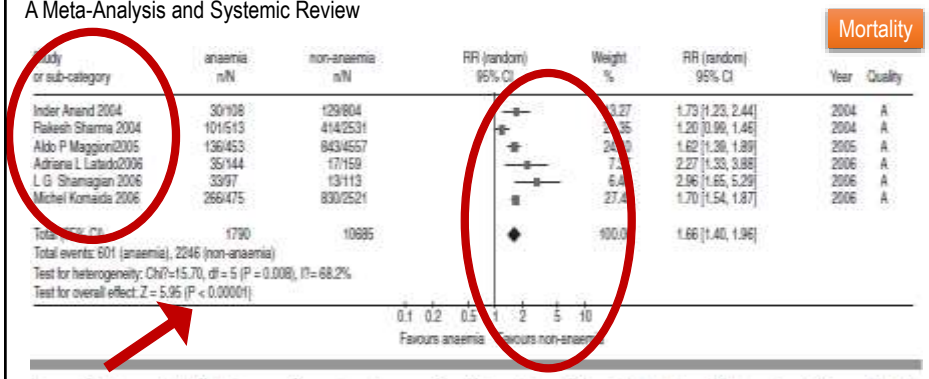
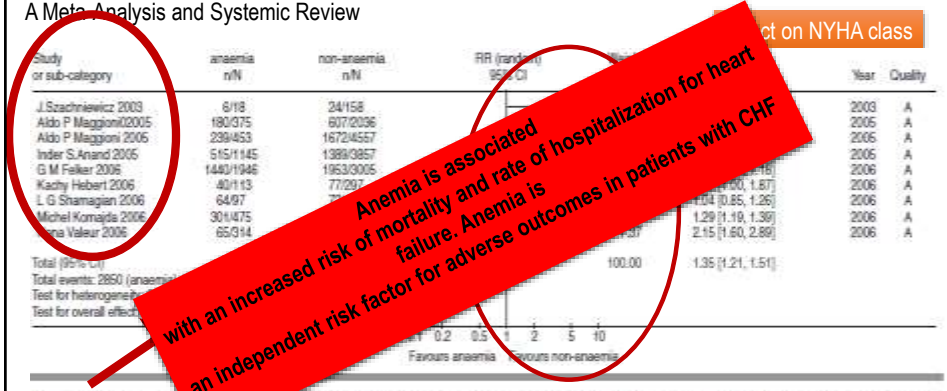


Figure 2. Meta-analysis of the impact of anemia on the mortality of chronic heart failure. RR, relative risk in random-effect model. RR (random) indicates relative risk in random-effect model; CI, confidence interval.

Congest Heart Fail. 2009;15:123–130

The Impact of Anemia on the Prognosis of Chronic Heart Failure

A Meta-Analysis and Systemic Review



Anemia is associated with an increased risk of mortality and rate of hospitalization for heart failure. Anemia is an independent risk factor for adverse outcomes in patients with CHF

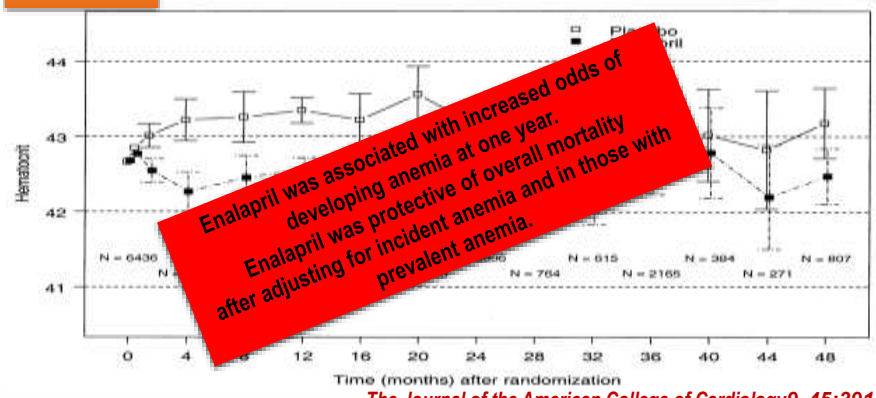
Figure 3. Meta-analysis of the impact of anemia on the risk of new-onset effect of New York Heart Association (NYHA) III or IV vs I or II. RR (random) indicates relative risk in random-effect model; CI, confidence interval.

Congest Heart Fail. 2009;15:123–130

Drug contributing to failure of anemia management in heart failure

Angiotensin-Converting Enzyme Inhibitor as a Risk Factor for the Development of Anemia

SOLVED trail



The Journal of the American College of Cardiology9–45:391;2005

Management of anemia in acute decompensated heart failure

Optimum haemoglobin threshold for transfer blood in acute setting of anemia

Hemoglobin 8 to 10 g/dL – Transfusion **generally not indicated**, but **may** be considered for some populations (eg, those with **symptomatic anemia**, ongoing bleeding, acute coronary syndrome with ischemia, and hematology/oncology [illegible]th severe thrombocytopenia who are at risk of bleeding)

Controversial !!!

Hemoglobin 7-6 g/dl :restrictive transfusion

Hemoglobin <6 g/dl :transfusion recommended

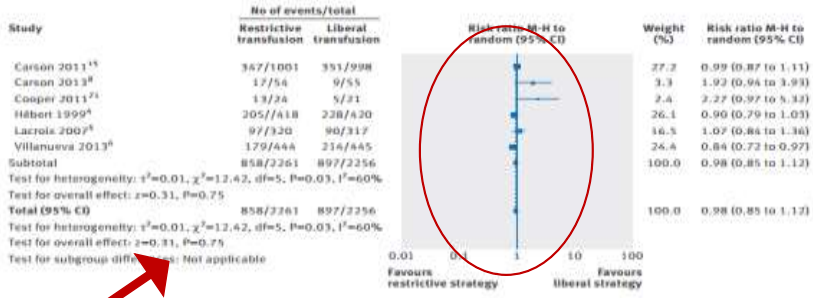
Clinical practice guidelines from the American Association of Blood Banks (AABB) : Red blood cell transfusion thresholds and storage.
Journal of American Medical Association. 2016;316(19):2025-2035

Management of anemia in acute decompensated heart failure

Optimum haemoglobin threshold for transfer blood in acute setting of anaemia

Restrictive versus liberal transfusion strategy for red blood cell transfusion:
Systematic review and Meta-analysis

Mortality



The British medical journal 2015;350:h1354

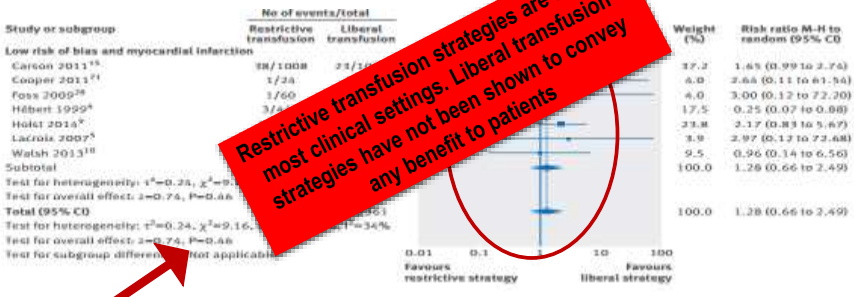
Management of anemia in acute decompensated heart failure

Optimum haemoglobin threshold for transfer blood in acute setting of anaemia

Restrictive versus liberal transfusion strategy for red blood cell transfusion:
Systematic review and Meta-analysis

Myocardial infarction

Restrictive transfusion strategies are safe in most clinical settings. Liberal transfusion strategies have not been shown to convey any benefit to patients



British medical journal 2015;350:h1354

Management of anemia in acute decompensated heart failure

Hypocalcaemia management due to massive blood transfusion

Calcium chloride may be **preferable** to **calcium gluconate** in the presence of abnormal liver function, since citrate metabolism is decreased, resulting in slower release of ionized calcium

If 10 percent **calcium gluconate** is used, 10 to 20 mL should be given intravenously (into another vein) for each 500 mL of blood infused.

If 10 percent **calcium chloride** is used, only 2 to 5 mL per 500 mL of blood should be given.

British Journal of Hematology, 135, 634–641

Management of anemia in chronic heart failure

Effects of erythropoiesis-stimulating agents on heart failure patients with anemia: a meta-analysis

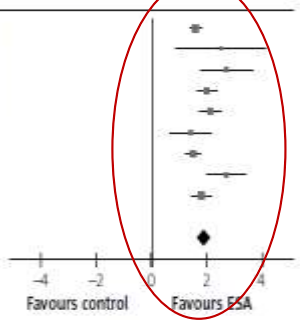
Increase in Hg

A. Comparison of hemoglobin

Study or subgroup	ESAs Mean	ESAs SD	ESAs Total	Control Mean	Control SD	Control Total	Weight (%)	Mean difference IV, random, 95% CI
Ghali 2008	1.9	1	162	0.3	1	157	17.9	1.60 (1.38, 1.82)
Kourea 2008	1.6	1.3	21	−0.9	3.5	20	2.1	2.50 (0.87, 4.13)
Mancini 2003	3.3	0.9	18	0.6	1.2	8	5.3	2.70 (1.77, 3.63)
Palazzuoli 2006	1.2	0.5	20	−0.8	0.6	18	14.6	2.00 (1.65, 2.35)
Palazzuoli 2007	2	0.7	26	−0.1	0.7	25	13.9	2.10 (1.72, 2.48)
Parissis 2008	1.8	1.05	21	0.4	1	11	7.3	1.40 (0.66, 2.14)
Ponikowski 2007	2.4	0.4	19	0.9	0.5	22	16.5	1.50 (1.22, 1.78)
Silverberg 2001	2.6	1.2	16	−0.1	0.8	16	7.7	2.70 (1.99, 3.41)
van Veldhuisen 2007	1.8	0.95	110	0	1.15	55	14.7	1.80 (1.45, 2.15)
Total (95% CI)			413			332	100.0	1.89 (1.64, 2.14)

Heterogeneity: $\tau^2 = 0.08$; $\chi^2 = 22.69$, $df = 8$ ($p = 0.004$); $I^2 = 65\%$

Test for overall effect: $Z = 14.90$ ($p < 0.00001$)



Advances Interventional Cardiology 2016; 12, 3 (45): 247–253

Management of anemia in chronic heart failure

Effects of erythropoiesis-stimulating agents on heart failure patients with anemia: a meta-analysis

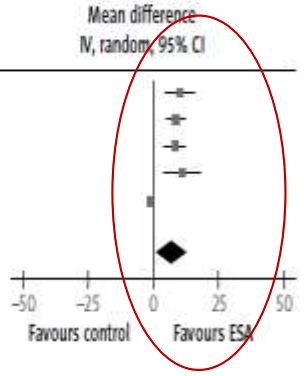
Increase in NYHA

B. Comparison of LVEF

Study or subgroup	ESAs Mean	ESAs SD	ESAs Total	Control Mean	Control SD	Control Total	Weight (%)	Mean difference IV, random, 95% CI
Kourea 2008	5	5	21	−5	12	20	18.9	10.00 (4.32, 15.68)
Palazzuoli 2007	6.8	6.75	26	−1.5	6.05	25	20.9	8.30 (4.78, 11.82)
Parissis 2008	5	6	21	−3	5.5	11	20.4	8.00 (3.86, 12.14)
Silverberg 2001	5.5	12.3	16	−5.4	7.3	16	17.6	10.90 (3.89, 17.91)
van Veldhuisen 2007	−0.02	0.91	110	1.27	1.29	55	22.3	−1.29 (−1.67, −0.91)
Total (95% CI)			194			127	100.0	6.88 (0.49, 13.28)

Heterogeneity: $\tau^2 = 47.78$; $\chi^2 = 72.75$, $df = 4$ ($p < 0.00001$); $I^2 = 95\%$

Test for overall effect: $Z = 2.11$ ($p = 0.03$)



Advances Interventional Cardiology 2016; 12, 3 (45): 247–253

Management of anemia in chronic heart failure

Effects of erythropoiesis-stimulating agents on heart failure patients with anemia: a meta-analysis

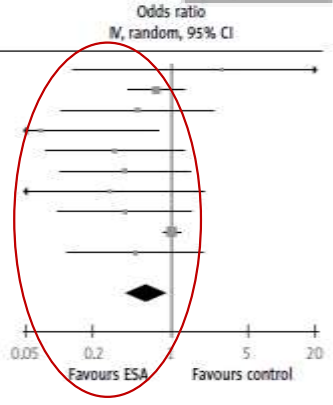
Hospitalization

A. Heart failure hospitalizations

Study or subgroup	ESAs Events	ESAs Total	Control Events	Control Total	Weight (%)	Odds ratio IV, random, 95% CI
Cleland 2005	3	18	0	6	1.9	2.94 (0.13, 65.26)
Ghali 2008	25	162	31	157	21.6	0.74 (0.42, 1.32)
Kourea 2008	3	21	5	20	6.2	0.50 (0.10, 2.44)
Mancini 2003	1	16	4	8	2.9	0.07 (0.01, 0.78)
Palazzuoli 2006	4	20	8	18	7.3	0.31 (0.07, 1.31)
Palazzuoli 2007	4	26	8	25	7.9	0.39 (0.10, 1.50)
Parissis 2008	2	21	3	11	4.3	0.28 (0.04, 2.01)
Ponikowski 2007	4	19	9	22	7.6	0.39 (0.10, 1.55)
Swedberg 2013	314	1136	311	1142	33.1	1.02 (0.85, 1.23)
van Veldhuisen 2007	4	110	4	55	7.3	0.48 (0.12, 2.00)
Total (95% CI)		1549		1464	100.0	0.61 (0.39, 0.94)
Total events	364		383			

Heterogeneity: $\tau^2 = 0.14$, $\chi^2 = 14.68$, $df = 9$ ($p = 0.10$), $I^2 = 39\%$

Test for overall effect: $Z = 2.25$ ($p = 0.02$)



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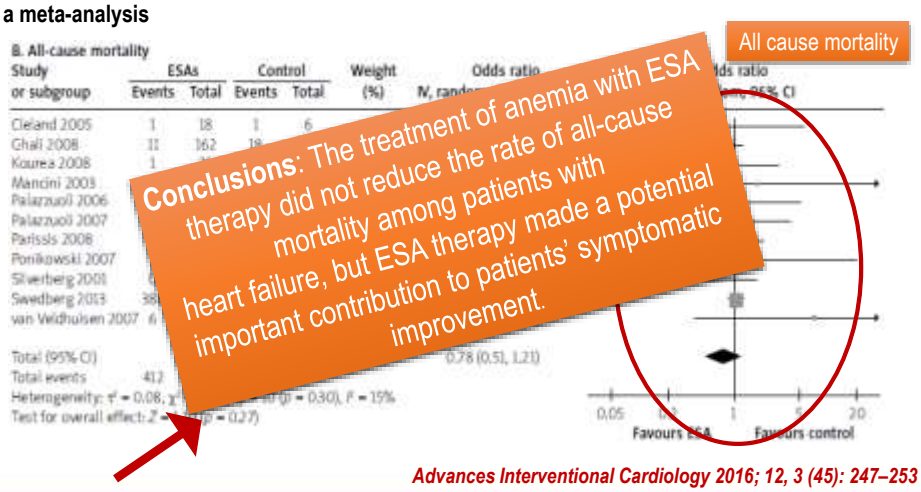
Management of anemia in chronic heart failure

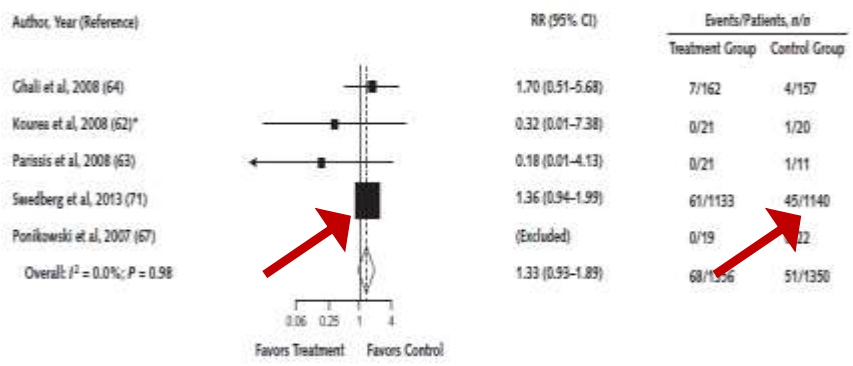
Effects of erythropoiesis-stimulating agents on heart failure patients with anemia: a meta-analysis



Advances Interventional Cardiology 2016; 12, 3 (45): 247–253

Management of anemia in chronic heart failure

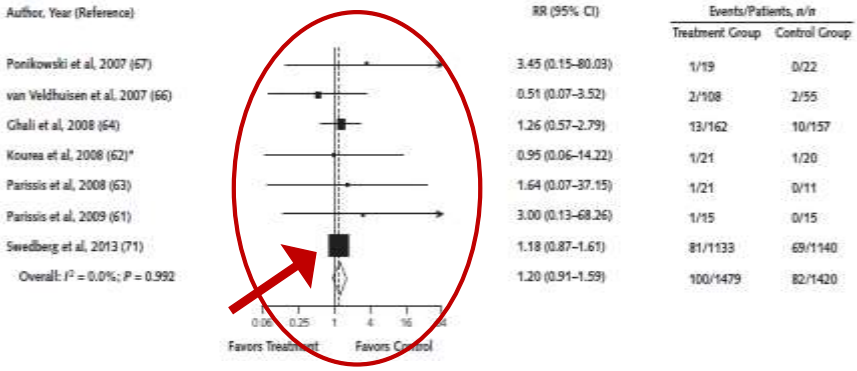
Cerebrovascular event



Annals of Internal Medicine. 2013;159:746-757

Management of anemia in chronic heart failure

Hypertension



Annals of Internal Medicine. 2013;159:746-757

Management of anemia in chronic heart failure

Venous thromboembolic

Annals of Internal Medicine. 2013;159:746-757

Management of anemia in chronic heart failure

Iron therapy for the treatment of iron deficiency in chronic heart failure

Intravenous or oral?

Oral Iron

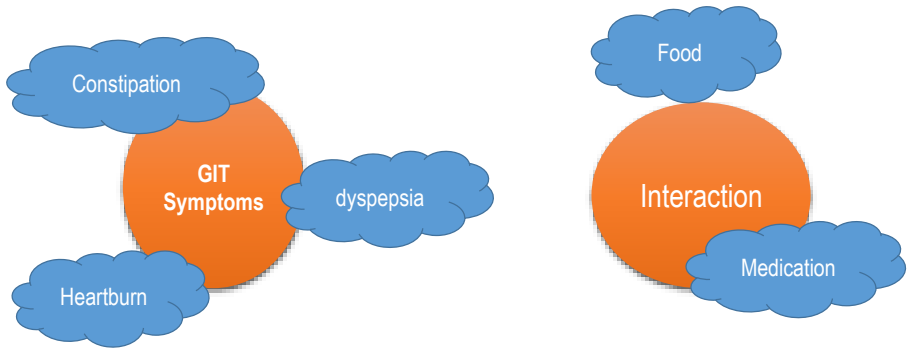
- Oral iron therapy is relatively **inexpensive** and **widely used**
- Oral iron is most frequently given in the form of **ferrous (Fe[II])** salts, such as ferrous sulfate

European Journal of Heart Failure (2015) 17, 248–262

Management of anemia in chronic heart failure

Iron therapy for the treatment of iron deficiency in chronic heart failure

Oral Iron



European Journal of Heart Failure (2015) 17, 248–262

Management of anemia in chronic heart failure

Iron therapy for the treatment of iron deficiency in chronic heart failure

Oral Iron

Difficult balance between maximizing uptake and minimizing gastrointestinal side effects.

European Journal of Heart Failure (2015) 17, 248–262

Management of anemia in chronic heart failure

Iron therapy for the treatment of iron deficiency in chronic heart failure

Oral Iron

Dosing consideration

The median required dose of iron to achieve iron repleti… in iron-deficient patients with heart failure is **1000** mg

Given that a typical dose o… on/day

Best scenario

50 day

Worse scenario

100 day

European Journal of Heart Failure (2015) 17, 248–262

Management of anemia in chronic heart failure

Iron therapy for the treatment of iron deficiency in chronic heart failure

Oral Iron

IRONOUT: Oral Iron Therapy for Heart Failure With Reduced Ejection Fraction: Design and Rationale for Oral Iron Repletion Effects on Oxygen Uptake in Heart Failure

Carried out in **225** patients, investigated the effect of **oral iron** polysaccharide (150 mg twice daily) compared with matching **placebo**. IRONOUT HF is an NIH-sponsored multi-center, randomized, double-blinded, placebo-controlled trial, which enrolled patients between September **2014** and November **2015** at 23 U.S. sites

Circulatory Heart Failure. ***2016 May;9(5)***

Management of anemia in chronic heart failure

Iron therapy for the treatment of iron deficiency in chronic heart failure

Oral Iron

IRONOUT: Oral Iron Therapy for Heart Failure With Reduced Ejection Fraction: Design and Rationale for Oral Iron Repletion Effects on Oxygen Uptake in Heart Failure

- The primary endpoint was the change in **exercise capacity** as measured by peak oxygen consumption from baseline to week 16.
- Secondary endpoints included changes in **distance walked in six minutes**, oxygen kinetics, ventilator efficiency, and a quality of life score.

Neither primary nor secondary endpoints differed significantly between groups

Circulatory Heart Failure. ***2016 May;9(5)***

Management of anemia in chronic heart failure

Iron therapy for the treatment of iron deficiency in chronic heart failure

Intravenous Iron

A series of I.V iron complexes has been developed which enclose an iron-containing core within a carbohydrate shell, stabilizing the structure and controlling the release of iron

European Journal of Heart Failure (2015) 17, 248–262

Management of anemia in chronic heart failure

Iron therapy for the treatment of iron deficiency in chronic heart failure

Intravenous Iron

Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: *Meta-analysis*

- Tobli *et al.* 2007
- Okonko *et al.* 2008 **FERRIC-HF**
- Beck-da-Silva *et al.* 2013 **IRON-HF** study
- Anker *et al.* 2009 **FAIR-HF** study
- Ponikowski *et al.* 2015 **CONFIRM-HF** study

…l of Heart Failure (2016) 18, 786–795

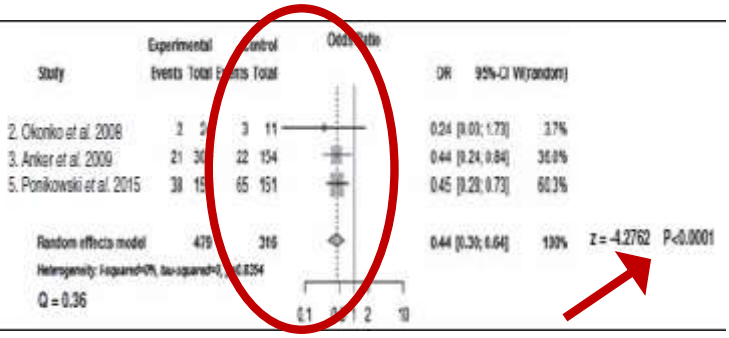
Management of anemia in chronic heart failure

Iron therapy for the treatment of iron deficiency in chronic heart failure

Intravenous Iron

Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure:
Meta-analysis

All-cause death or cardiovascular hospitalization



European Journal of Heart Failure (2016) 18, 786–795

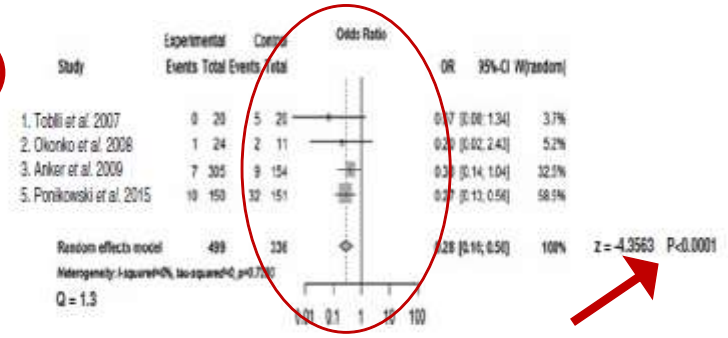
Management of anemia in chronic heart failure

Iron therapy for the treatment of iron deficiency in chronic heart failure

Intravenous Iron

Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure:
Meta-analysis

HF hospitalization



European Journal of Heart Failure (2016) 18, 786–795

EGYPTIAN SOCIETY OF CARDIOLOGY
CardioEgypt2017

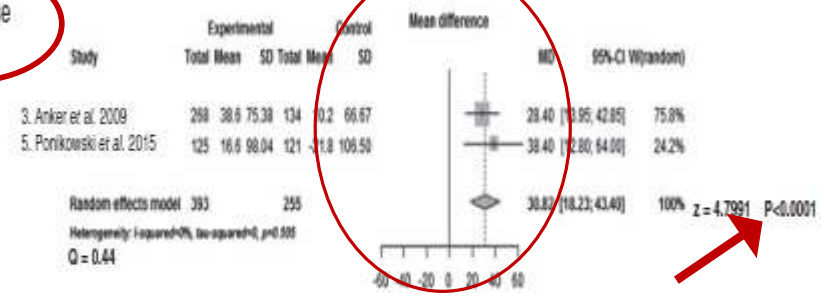
Management of anemia in chronic heart failure

Iron therapy for the treatment of iron deficiency in chronic heart failure

Intravenous Iron

Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure:
Meta-analysis

6MWT distance



European Journal of Heart Failure (2016) 18, 786–795

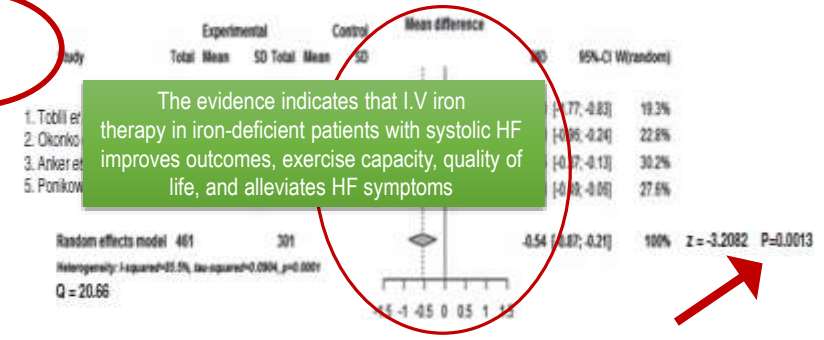
Management of anemia in chronic heart failure

Iron therapy for the treatment of iron deficiency in chronic heart failure

Intravenous Iron

Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure:
Meta-analysis

NYHA class



The evidence indicates that I.V iron therapy in iron-deficient patients with systolic HF improves outcomes, exercise capacity, quality of life, and alleviates HF symptoms

European Journal of Heart Failure (2016) 18, 786–795

ClinicalTrials.gov NCT00384657

Future research

The Effects of Intravenous Iron Therapy for Anemia Correction in Patients With Severe Chronic Heart Failure and Concomitant Moderate Chronic Kidney Disease

Trial date

Estimated Enrollment: 200
Study Start Date: January 2008
Estimated Study Completion Date: June 2021
Estimated Primary Completion Date: December 2019 (Final data collection date for primary outcome measure)

ClinicalTrials.gov NCT00384657

Future research

The Effects of Intravenous Iron Therapy for Anemia Correction in Patients With Severe Chronic Heart Failure and Concomitant Moderate Chronic Kidney Disease

Inclusion Criteria

Persistent severe CHF left ventricular ejection fraction (echocardiography) less than 40%;

Stable stage 3 chronic kidney disease: estimated GFR between 30-59mL/min/1.73m2

Mild to moderate anemia: hemoglobin levels < 12g/dL

iron deficiency: absolute (serum ferritin < 100ng/mL) or functional (serum ferritin 100-300ng/mL and transferrin saturation < 20%)

ClinicalTrials.gov NCT00384657

Future research

The Effects of Intravenous Iron Therapy for Anemia Correction in Patients With Severe Chronic Heart Failure and Concomitant Moderate Chronic Kidney Disease

Trial design

Group I (treatment group)
Subjects assigned to this group will receive **intravenous iron** (ferric sucrose product Venofer® 2%, 5mL/ampoule) in a starting dose of 200mg (2 ampoules) diluted in 150mL 0.9% NaCl solution, over 60 minutes, **once a week** for the **first four** administrations, and then **every other week** until hemoglobin levels reach 12g/dL. Then, iron dose will be adjusted to 1 ampoule at 2-4 weeks interval, as needed to maintain these levels with serum ferritin ≤500ng/mL

Group II (control group)
Subjects assigned to this group will **continue their conventional treatment for CHF as needed**, without iron supplementation

ClinicalTrials.gov NCT00384657

Future research

The Effects of Intravenous Iron Therapy for Anemia Correction in Patients With Severe Chronic Heart Failure and Concomitant Moderate Chronic Kidney Disease

Original Primary Outcome Measures

- Percentage of patients achieving **target hemoglobin level** (> 12g/dL) at the end of the study
- Percentage of the patients reaching a better **NYHA functional** class at the end of the study
- Absolute **change in estimated glomerular filtration rate** from baseline at the end of the study

Take home message

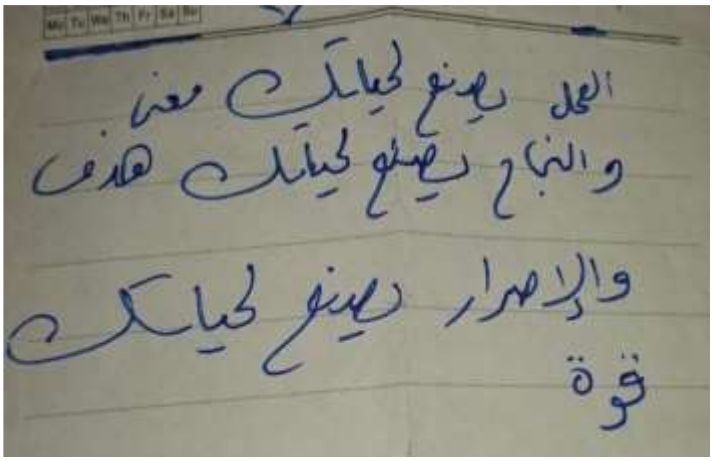
Anemia in heart failure associated is with an increased risk of mortality and rate of hospitalization

Enalapril was associated with developing anemia at one year

Restrictive transfusion strategies are safe in most clinical settings.

The treatment of anemia with ESA therapy did not reduce the rate of all-cause mortality, but made lead to patients' symptomatic improvement taking into consideration safety profile

Results of current literature indicates that I.V iron therapy HF improves outcomes, exercise capacity, and quality of life



Thank you